Protocol Overview

Study AC-060A202: CONTROL

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ACTELION

Phase IIb Study AC-060A202
Study Design

- A Phase 2b, multi-center, double-blind, placebo-controlled, parallel-group study to establish proof-of-concept and explore the efficacy of different doses of ACT-129968 in adult patients with partly controlled asthma

- 412 patients to be recruited → 103 patients/arm

- 120 Patients in the PK Sub-study → 30 patients/arm

- Primary Endpoint:

  Change from baseline to week 12 in pre-bronchodilator FEV1 % of predicted (FEV1%oP) [1000 mg b.i.d. dose]

AC-060A202 study

CONTROL: CRTH2 AntagONist TReatment to contrOL asthma

- Population: Adult patients (age: 18-65) with partly controlled asthma
- Dose/ duration: ACT-129968 100, 500 or 1000 mg/ b.i.d. or placebo (4 capsules) over 12 weeks treatment followed by 2 weeks run-out period
- Location: Approximately 100 centers
- Countries: Australia, Bulgaria, Germany, Hungary, Israel, Poland, Serbia, Singapore, South Africa, Sweden, Russia, Ukraine, USA
- Study-mandated and supplied concomitant asthma medications:
    - Reliever medication: Salbutamol/albuterol
- FPFV – November 2010

Addendums to ICF

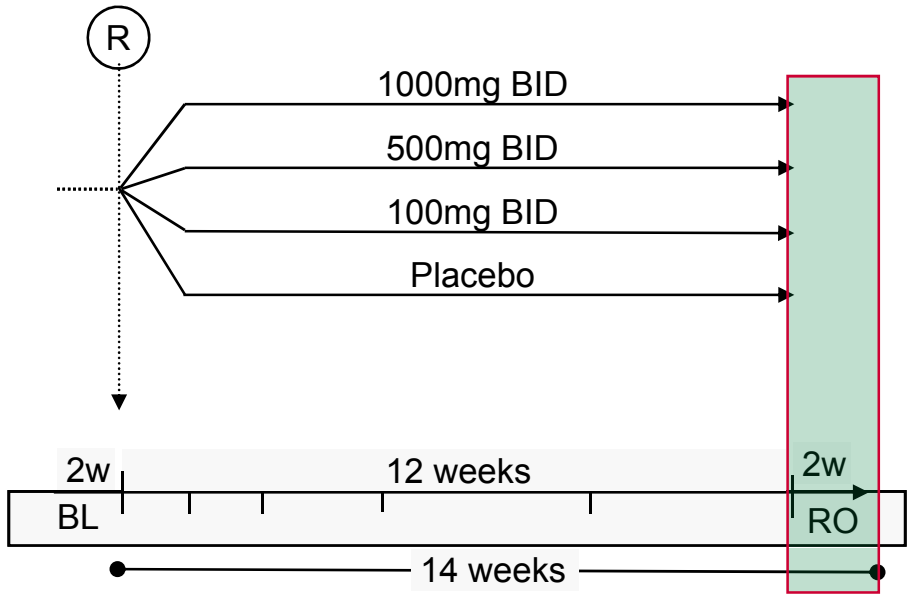
- PK-CM sub-study only at specific sites
  - Must sign Addendum 1- **Pharmacokinetic-Cardiac Monitoring Sub-study**

- Single nucleotide polymorphisms (SNPs) (DNA) blood sample
  - Must sign Addendum 2 - **Voluntary DNA testing**
  - Check CRF to ensure question regarding retention/destruction of DNA sample is correct to source data

Patient Population

- Allergic asthma (positive skin prick/RAST test)
- Responsive to bronchodilator (reversibility testing)
- Partly controlled (ACQ $\geq$1.5)
- Not taking ICS (Inhaled corticosteroids) for at least 4 weeks
  - Looking for newly diagnosed asthmatics or
  - Patients who do not take ICS or
  - Patients who are not compliant with taking ICS

Study Design/Period



Phase IIb Study AC-060A202
Patients characteristic / Inclusion

- Males and females aged 18 to 65 years consenting to study participation.
- Women of childbearing potential must:
  - Have a negative serum pregnancy test at screening and a negative urine pregnancy test at randomization (before the first study drug intake). Both tests must be separated by at least 16 days.
  - Agree to use a reliable method of contraception from the screening visit until at least 1 month after study drug discontinuation.
  - Non-childbearing potential defined as postmenopausal (i.e., amenorrhea for 1 yr) or surgically or naturally sterile.
- Diagnosis of asthma according to GINA Guidelines [2009].
- FEV1 ≤ 85 % of predicted normal value at Visit 1 and confirmed at Visit 2.
- Reversibility of airway obstruction of ≥ 12% and ≥ 200 mL, demonstrated during the screening period.
- Asthma Control Questionnaire (ACQ) score ≥ 1.5
- Positive skin prick or RAST tests, demonstrated at Visit 1

Phase IIb Study AC-060A202

Patients characteristic / Main Exclusion

- Pregnant or lactating women.
- Any asthma exacerbation requiring treatment with systemic corticosteroids within the last 3 months.
- Any hospital admission for asthma within the last 6 months.
- Smoking within the last year or more than 10 pack-years during life.
- QTcF > 450 msec (males) and QTcF > 470 msec (females) at either Visit 1 or Visit 2
- Inability to perform acceptable and repeatable spirometry according to ATS/ERS criteria

Phase IIb Study AC-060A202
Patients characteristic / Main Exclusion

- Vaccination with live-vaccines within 3 months prior to Visit 1 and during study participation.
- Bacterial or viral infection of the upper or lower respiratory tract, that did not resolve at least 4 weeks before screening.
- History of chronic pulmonary disease (other than asthma) such as COPD, fibrosis, tuberculosis or sarcoidosis.
- Congenital or acquired severe immunodeficiency or known HIV infection.
- Known history or clinical evidence of hepatitis B or C and/or positive hepatitis serology, indicating acute or chronic hepatitis B or C.

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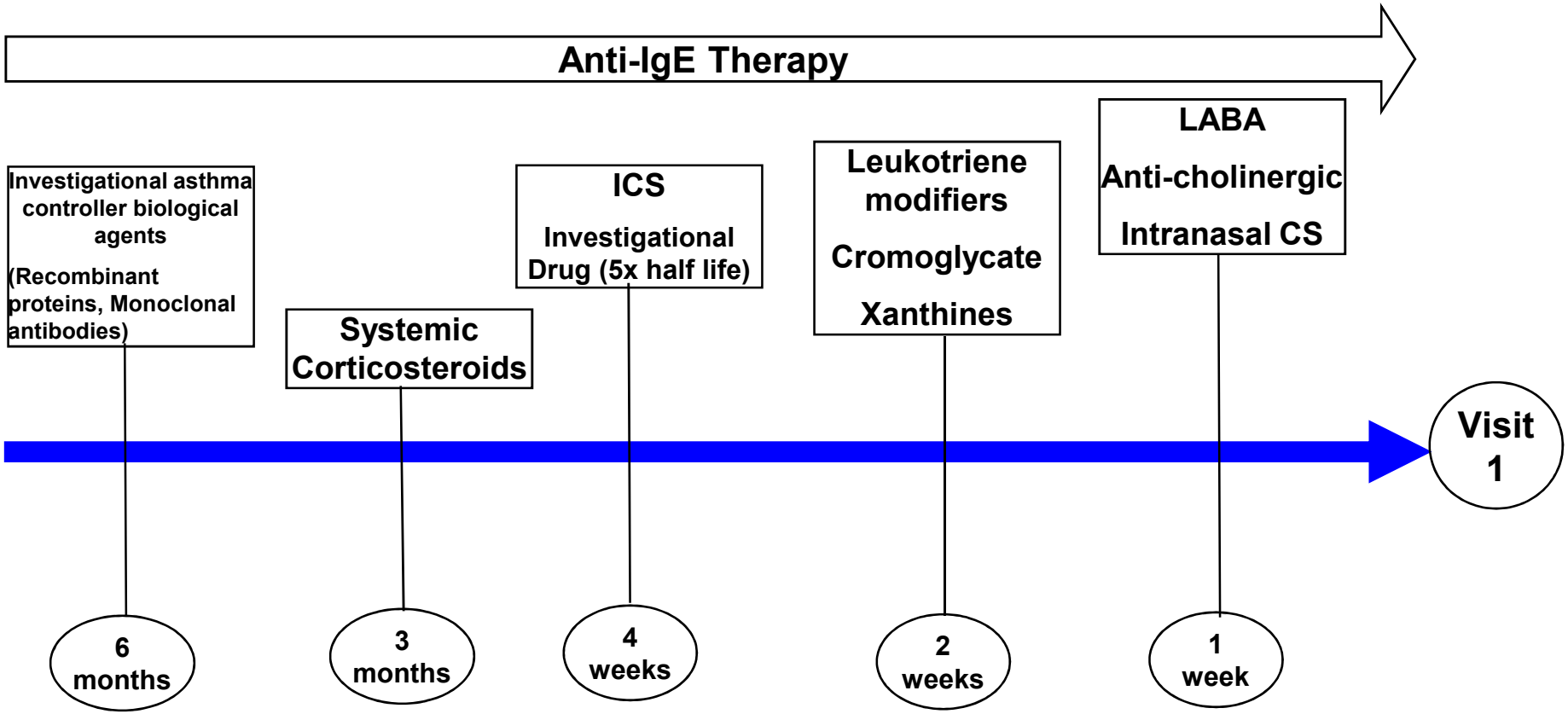
Exclusion Criteria:



Phase IIb Study AC-060A202
Primary Endpoint & Sample Size

Primary Endpoint: change in FEV1 % of predicted from baseline at 12 weeks

- FEV1 will be controlled at study entry
  - FEV1 ≤85% predicted
  - expected improvement (in between montelukast and ICS): 6% of predicted

- asthma control (by ACQ) as important parameter included as secondary endpoint

Sample Size Estimation

- Effect Size to be detected
  - 6% of predicted
  - SD: 13 % of predicted
  - alpha: 0.05

- Power of 90% for ACT-129968 1000 mg BID vs. PBO
- 100 Patients per Arm

source: Malmstrom etal Ann Intern Med 130:487, 1999
Pinnas et al. JAsthma 42:865 2005

Phase IIb Study AC-060A202
Secondary and Exploratory Endpoints

- Control of asthma by ACQ*
- Lung function on remaining time points
- Time to initiation of additional asthma treatment
- Diary Variables (PEF, asthma symptoms, use of reliever medication)
- Clinical Asthma Exacerbation
- Nasal symptoms by Visual Analog Scale (VAS)
- Asthma related Quality of Life [AQLQ(S)*]
- Inflammatory parameter in peripheral blood
- ACT-129968 trough plasma level
- ACT-129968 12-hour profiles (sub study)

* Asthma Control Questionnaire (ACQ)
Standardized version of the Asthma
Quality of Life Questionnaire [(AQLQ(S)]

Study assessments (1)

Table 1 Visit and assessment schedule (Part 1)

PERIODS	Name	SCREENING	TREATMENT					RUN-OUT	FOLLOW-UP
	Duration	2 weeks	12 weeks					2 weeks	2 weeks
VISITS	Name	Visit 1 Screening	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 End-of-Treatment	Visit 8 End-of-Study	Safety follow-up[1]
	Time	Week –2 (-4/+2 days)	Day 1	Week 1 (-1/+3 Days)	Week 2 (-1/+3 Days)	Week 4 (-1/+3 Days)	Week 8 (±3 Days)	Week 12 (±3 Days)	Week 14 (-1/+3 Days)	EOT + 30 Days (±1 Day)
Informed consent		X								
Inclusion/exclusion criteria/asthma diagnosis		X	X							
*Demography – medical history		X								
*Previous asthma treatments		X								
*Concomitant medications		X	X	X	X	X	X	X	X	
Physical examination		X	X	X	X	X	X	X	X	
*Body weight / height *(Height at Visit 1 only)*		X						X	X	
**ECG (supine 12-lead)		X	X	X	X	X	X	X	X	
*Blood pressure		X	X	X	X	X	X	X	X	
*SPT and **RAST		X						X		
**Spirometry (pre- & post-bronchodilator)		X	X	X	X	X	X	X	X	
Spirometry reversibility check		X	X[2]							
*ACQ		X	X	X	X	X	X	X	X	
*AQLQ(S)			X		X	X	X	X	X	
*Nasal symptoms (VAS)			X	X	X	X	X	X	X	
**PEF and diary review[3]		X	X	X	X	X	X	X	X	
Randomization			X							
Study drug dispensing[4]/return			X[5]	X	X	X	X	X		
Study drug swallowing test		X								
*Adverse events[6]			X	X	X	X	X	X	X	
*Serious adverse events[7]		X	X	X	X	X	X	X	X	X

For footnotes see next page.

Study assessments (2)

Table 2 Visit and assessment schedule (Part 2)

PERIODS	Nmae	SCREENING	TREATMENT						RUN-OUT	FOLLOW-UP
	Duration	2 weeks	12 weeks						2 weeks	2 weeks
VISITS	Name	Visit 1 Screening	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 End-of-Treatment	Visit 8 End-of-Study	Safety follow-up[1]
	Time	Week –2 (-4/+2 days)	Day 1	Week 1 (-1/+3 Days)	Week 2 (-1/+3 Days)	Week 4 (-1/+3 Days)	Week 8 (+3 Days)	Week 12 (+3 Days)	Week 14 (-1/+3 Days)	EOT + 30 Days (−1 Day)
**Blood sampling (hematology & blood chemistry)		X[2]	X	X	X	X	X	X	X	
**TSII, T3 and T4			X					X		
**Serum pregnancy test		X		X	X	X	X	X	X	
Urine pregnancy test (dipstick)			X[3]							
Urinalysis (dipstick testing)		X	X	X	X	X	X	X	X	
**Blood sampling PK[4]				X	X	X	X	X		
**Blood sampling (PD-1)[5]			X	X	X	X	X	X	X	
**Blood sampling CRTH2 mRNA levels (PD-2)			X					X		
**Blood sampling CRTH2 SNPs analysis (PD-3)[6]			X							

1. The SAE follow-up visit will be performed by phone 30 days after EOT.
2. No IgE testing at Visit 1.
3. Test must be performed at least 16 days after serum pregnancy test done at Visit 1.
4. Pharmacokinetics: trough (pre-morning dose) plasma concentrations of ACT-129968 for all patients.
5. Determination of IL-4, IL-5, IL-13 (PD-1) for all patients.
6. SNPs analysis of the CRTH2 (PD-3) coding and non-coding region (optional and voluntary). Patient must have signed Addendum 2 to the ICF.

** Electronically transferred to sponsor.

Order of Assessments - Overview

Following order should be followed and done prior to study drug dosing:

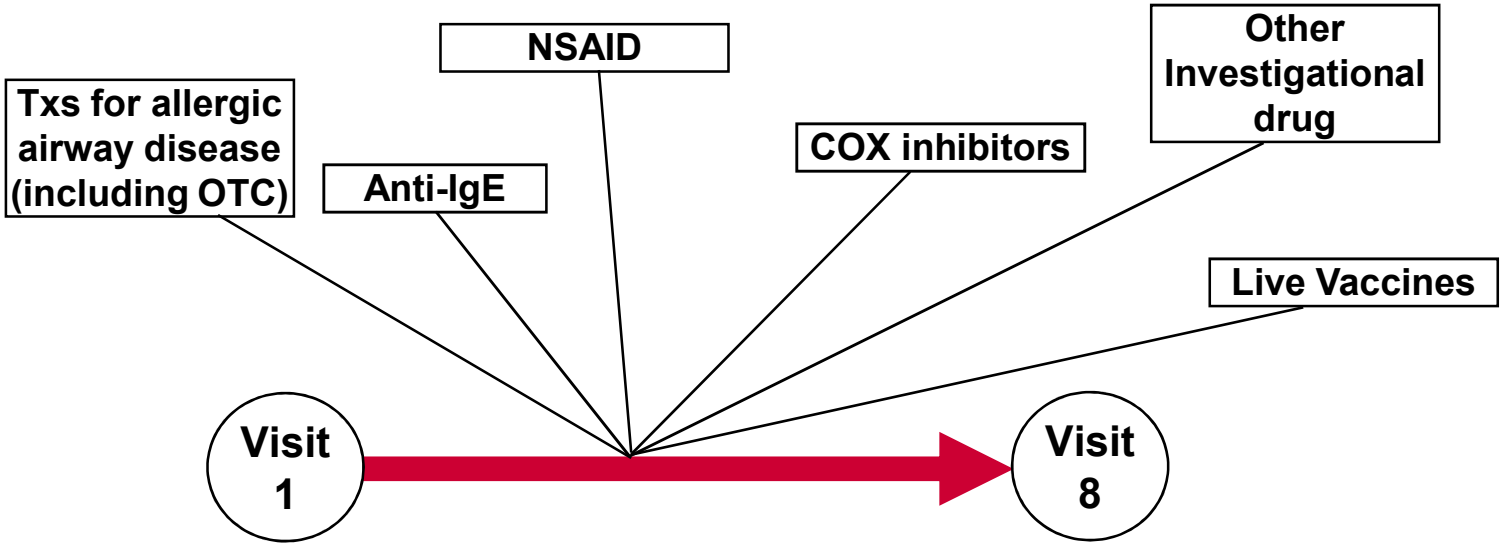
- ACQ, AQLQ(S), VAS nasal symptoms
- Blood Pressure
- ECG
- Physical examination
- Blood sampling, urinalysis
- Pulmonary function tests
  - At Visit 1 first perform e-Diary PEF and set the reference value
  - Then perform Pre-bronchodilator spirometry
    (Bronchodilation, using 400 µg of salbutamol)
  - Post-bronchodilator spirometry (15-45 min after the bronchodilation)

PD-1, PD-2, PD-3 Exploratory Blood Samples

- PD-1 IL
  - Asses major Th2 cell cytokines
- PD-2 CRTH2 mRNA
  - Assess CRTH2 expression levels
- PD-3 SNPs
  - Examining known CRTH2 polymorphisms (SNPs) linked to asthma severity
  - Must sign Addendum 2 of ICF (voluntary)

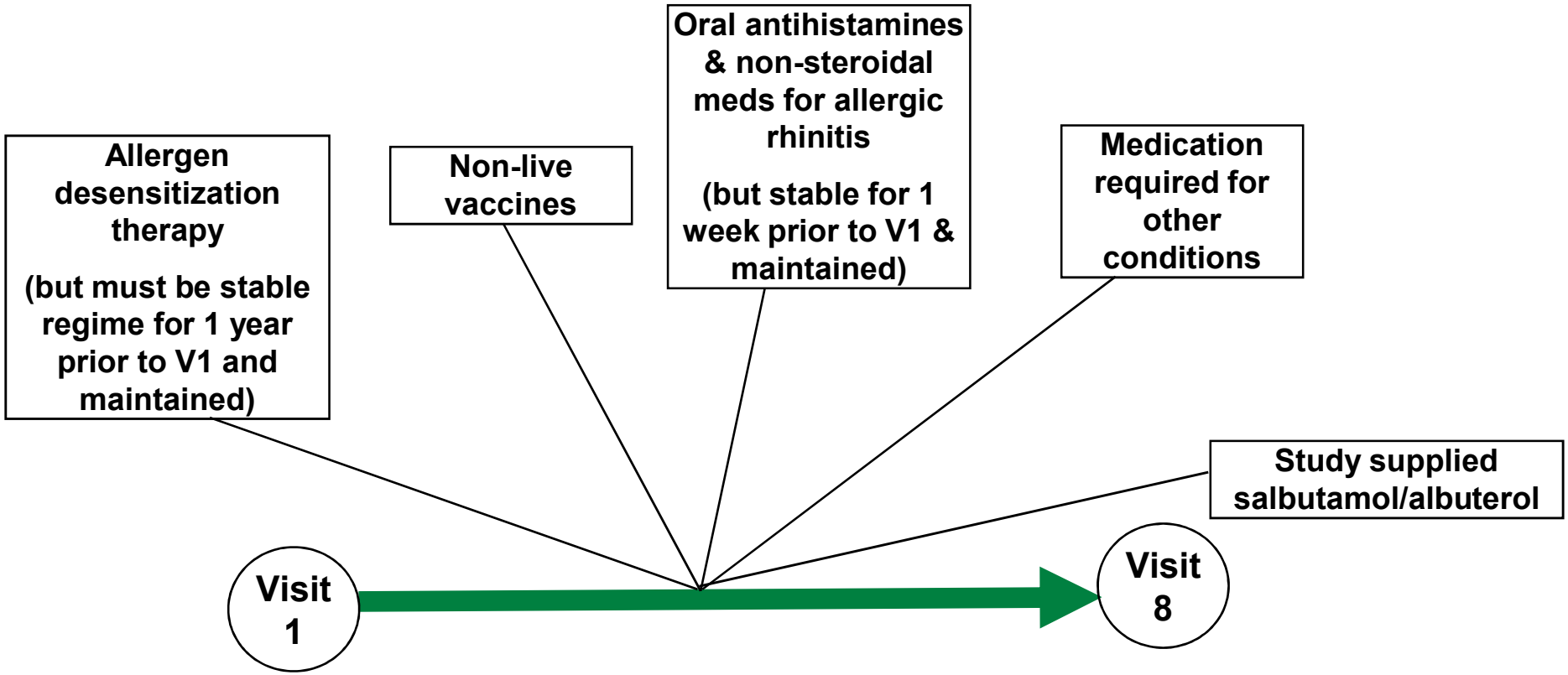
Phase IIb Study AC-060A202

Prohibited Concomitant Medication During Entire Study:



Phase IIb Study AC-060A202

Allowed Concomitant Medication During Entire Study:



Rescue Medication

- Salbutamol/albuterol (100 μg/puff, metered dose inhaler)
- With spacer
- Will be provided for each patient along with instructions

Premature discontinuation

Discontinuation during the treatment period

- The EOT Visit will be conducted.
- This will be considered the end of study for the patient.
- The 2-week run-out will not be conducted.
- Safety telephone calls must be conducted within 4-7 days

Discontinuation during the run-out period

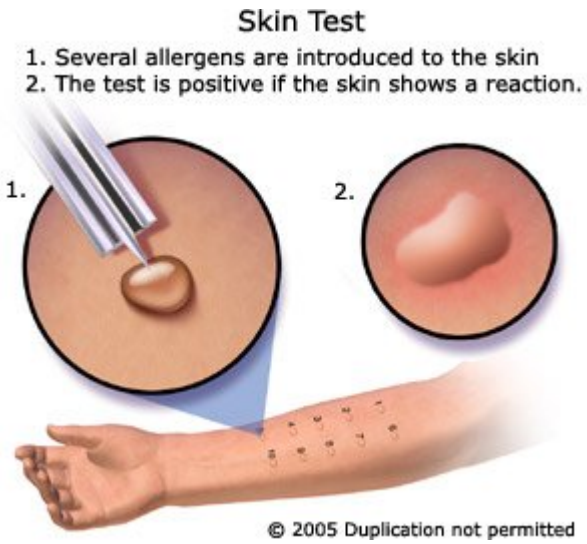
- The EOS Visit will be conducted.
- The 2-week run-out will not be continued.

30-days safety telephone call (for all patients) following last intake of study drug.

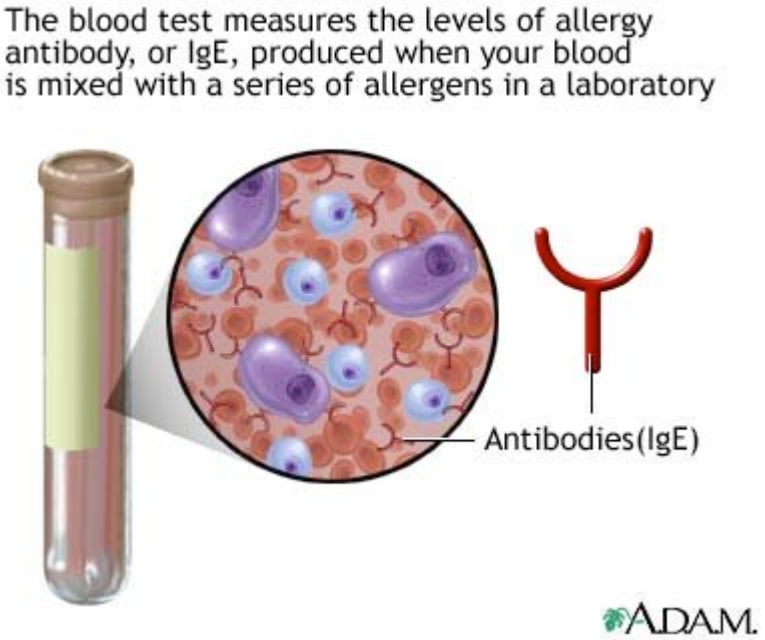
Efficacy Endpoints: Allergen Tests

Skin prick test and RAST

Skin Prick and RAST Testing



Skin Prick Test



RAST

Skin Prick Test (SPT)

- Skin test
- Performed at Visit 1
- Performed at Visit 7 **only if positive at Visit 1**
- Site uses their own allergen panel
- Site can use their standard procedure for SPT

RAST

- Blood test
- Performed at Visit 1& Visit 7
- Analyzed at central lab
- Allergen panel defined by Actelion
- Investigator can choose 2 more allergens in addition

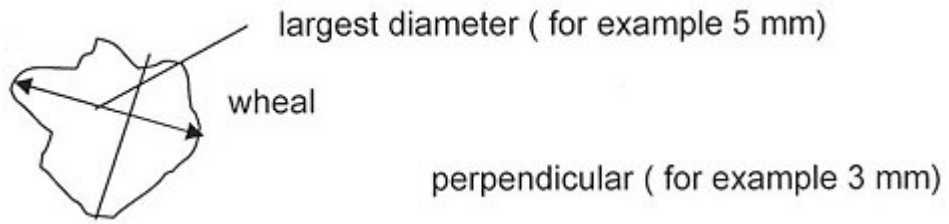
✓ **Patient must have EITHER a positive SPT or RAST to be randomized**

Skin Prick Test

- Site must supply their own panel of allergens and supplies
- Site can use their standard procedure or Actelion procedure
- Results must be calculated according to our procedure as follows:

✓ Formula*:

The mean wheal diameter = (largest + perpendicular diameter)/ 2



✓ A reaction is considered as “positive“ if the mean wheal diameter ≥ 3 mm greater than saline control

*Reference: GA²LEN (Global Allregy and Asthma European Network) website

Skin Prick Test result (1)

Scenario 1: Patient has positive SPT at Visit 1

- patient can be randomized
- record the largest allergen in CRF
- test only the largest allergen at Visit 7

Scenario 2: Patient has negative SPT at Visit 1

- patient should continue the 2 week screening phase
- RAST test must be positive to randomize the patient
- If both SPT and RAST test are negative then patient cannot be randomized
- If skin prick test is negative, do not repeat SPT at Visit 7

Skin Prick Test result (2)

Scenario 3: Patient is on allergen desensitization therapy at Visit 1

- If the largest wheal diameter is positive for the allergen used for desensitization therapy,
  - patient is considered having a positive SPT and can be randomized
  - record this allergen and wheal diameter in source data
  - enter the 2nd largest allergen in CRF (even if negative) and retest this allergen at Visit 7

RAST (Radioallergosorbent Test)

- RAST blood samples will be analyzed by central laboratory
- Standard regional 12 allergen panels are defined by Actelion:
  - ✓ US
  - ✓ Europe and Israel
  - ✓ Singapore
  - ✓ Australia
  - ✓ South Africa
- Investigator can choose 2 more allergens in addition from pick list
- RAST will be repeated at Visit 7 even if it is negative at Visit 1

RAST allergen panel for EU and Israel

- Cat
- Dog
- *Dermatophagoides pteronyssinus*
- *Dermatophagoides farinae*
- Blatella
- Tree mix Northern (Birch, hazel, alder)
- Plane
- Grass, mixed*
- Artemisia
- *Alternaria*
- *Cladosporium*
- *Aspergillus*

*Different grass mixes containing: *Dactylis glomerata*, *Lolium perenne*, *Festuca rubra*, *Poe pratensis*, *Phleum pratense*, *Secale cereale*, *Holcus lanatus*, *Anthoxanthum odoratum*, *Arrhenatherum elatius*, *Agrostis stolonifera*, *Alopecurus pratensis*, *Festuca pratensis.*

Heinzerling et al, *Allergy* 2005; **60**: 1287-1300

Efficacy Endpoints: Questionnaires

ACQ and AQLQ(S) / VAS

Questionnaires

- **ACQ (Asthma Control Questionnaire)**
  - Validated questionnaire that measures the adequacy of asthma control
- **AQLQ(S) (Asthma Quality of Life Questionnaire with Standardized Activities)**
  - Validated questionnaire that measures the physical, emotional, occupational and social problems that are most troublesome to adults with asthma

- To be filled in by patient – no help from anyone
- Filled in prior to any other assessments
- If at a later date you find entries are not completed, they cannot be updated later
- CRF form for corrections (can only be done on the day)

Nasal Symptoms VAS

Rate the severity of your total nasal symptoms over the last 24 hours by marking clearly and vertically across the line below:

Nasal symptoms,

not at all bothersome

Nasal symptoms,

extremely bothersome

Efficacy Endpoints: e-Diary + PEF meter

Asthma Symptom Score and PEF

Electronic Diary / PEF Meter – PiKoLogic (PiKo1)

Daily Recording by the Patient (morning & evening)

- **Asthma Symptom Score**

Daytime symptom score[+]	
0	No symptoms during the day
1	Symptoms for one short period during the day
2	Symptoms for 2 or more short periods during the day
3	Symptoms for most of the day which did not affect my normal daily activities
4	Symptoms for most of the day which did affect my normal daily activities
5	Symptoms so severe that I could not go to work/school or perform normal daily activities
Night-time symptom score[#]	
0	No symptoms during the night
1	Symptoms causing me to wake once or wake early
2	Symptoms causing me to wake twice or more (including waking early)
3	Symptoms causing me to be awake for most of the night
4	Symptoms so severe that I did not sleep at all

- **Daily use of reliever medication**
- **Time intake of study drug**
- **Time of breakfast and dinner**
- **Peak Expiratory Flow (PEF) measurement morning and evening**

PEF = Peak Exploratory Flow

- Measured during spirometry testing &
- Daily home electronic PEF meter
- Measured in:
  - L/sec in clinic (e.g. 5.2 L/sec)
  - L/min with PEF meter (e.g. 312 L/min)
  - FEV1 will also be measured
- Repeated 3 times at each session
- Forced, hard exhalation for a few seconds
- Alert Values to signal asthma deterioration
  - Patient to contact investigator

eDiary Alerts

1. **Alert value for Daily PEF** (i.e. 70% of patient baseline PEF value measured at the time of Visit 1): PEF drops below this value on at least 2 consecutive days

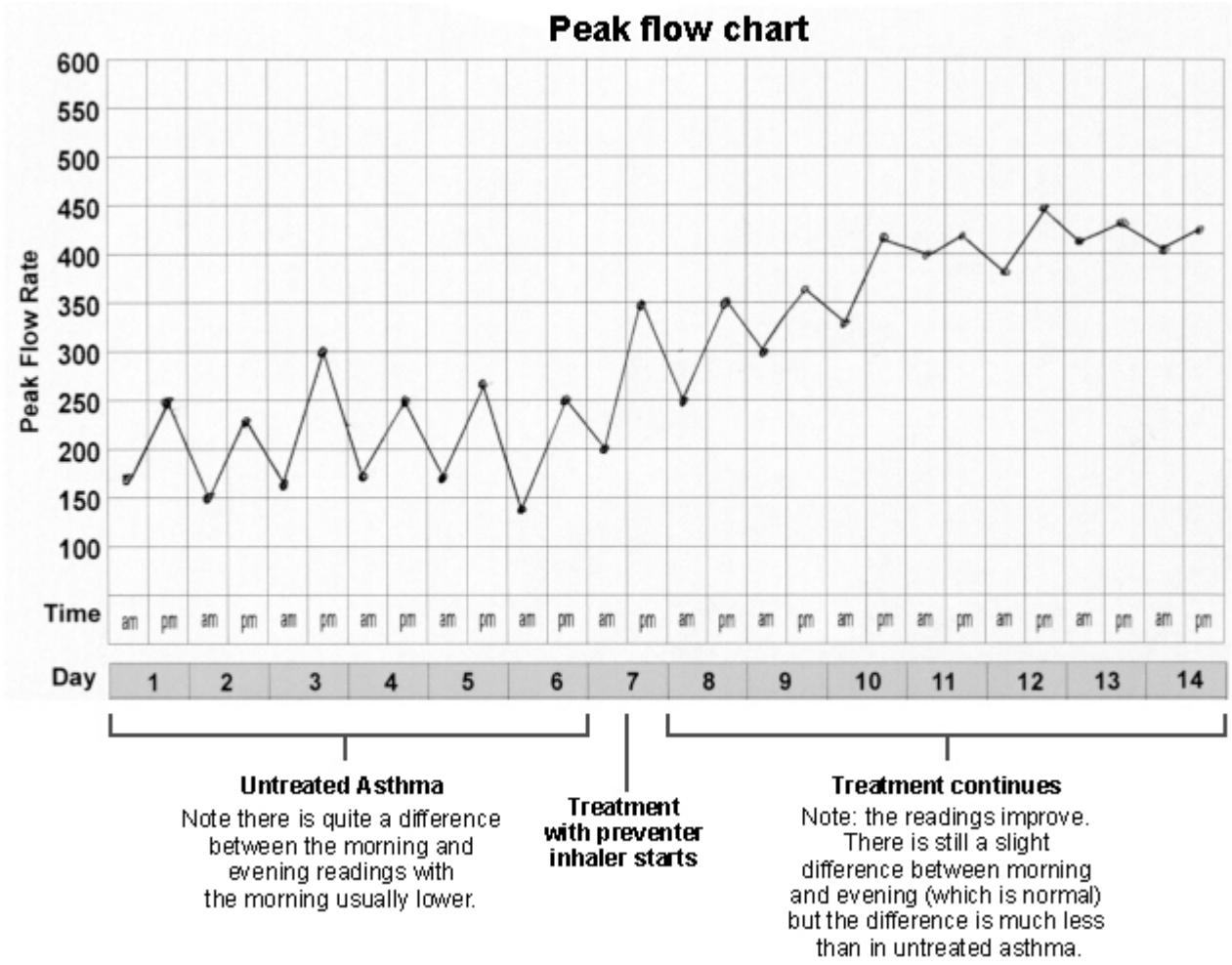
2. **Alert value for the asthma symptoms score:** a total daily asthma symptoms score is >6 on at least two consecutive days

3. **Alert value for intake of reliever medication:** the daily intake of reliever medication exceeds 8 occassions per 24 hours on at least two consecutive days

Monitoring Your Patient Through Electronic Diary/PiKo1

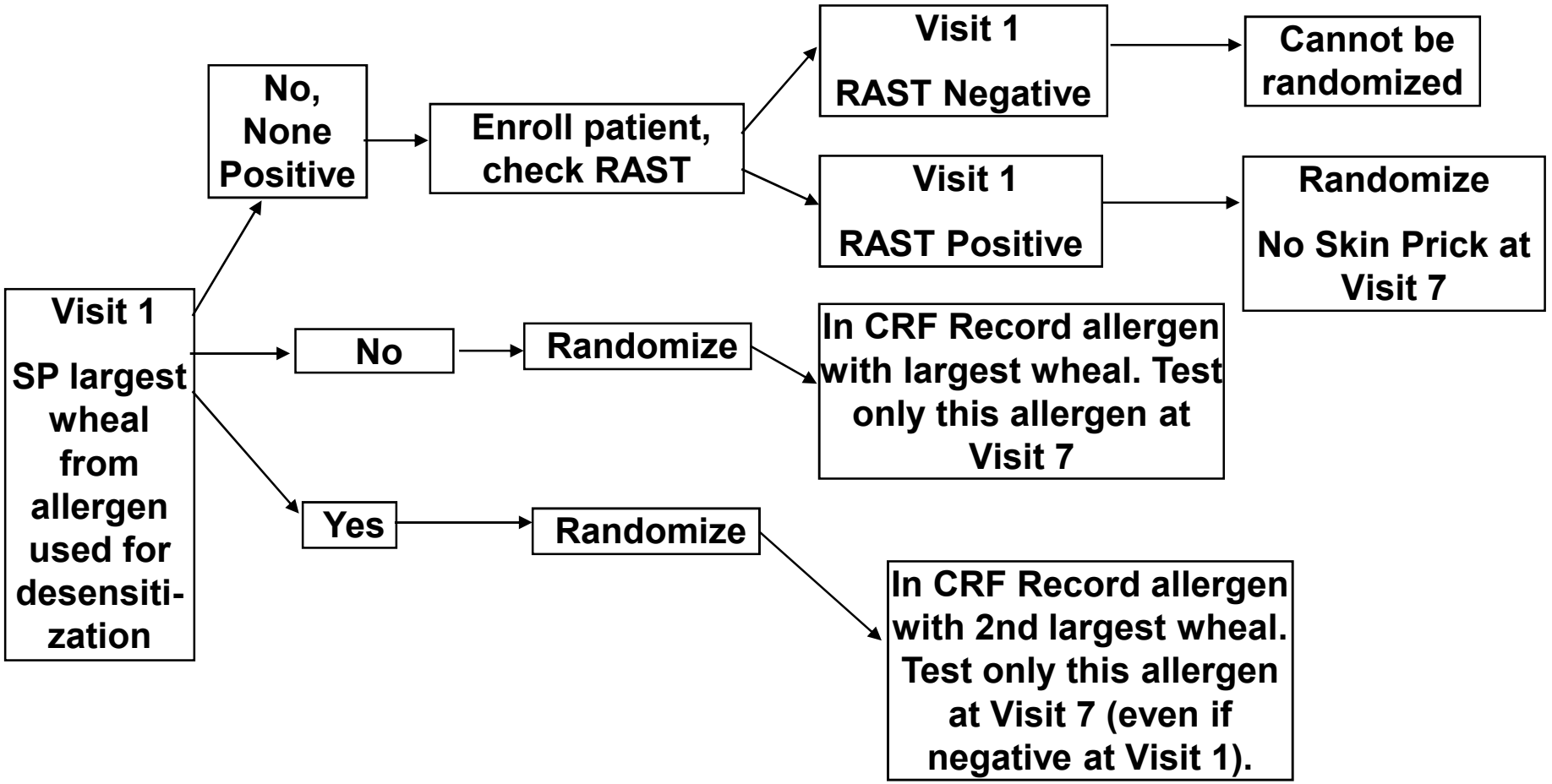
- **Training of Patient**
  - Initial training
  - Assess if patient still performing the PEF properly
  - Retrain patient at subsequent visits if required
  - Ensure patients answering all questions.
- **Check data at each visit to ensure patient results are stable**
  - Done via Web-portal
- **If patient triggers “alert value” a message will be sent to the investigator**
  - Patient should call investigator
  - Investigator should follow-up with the patient

Peak Flow Demo



Thank You!

Skin Prick Test (on allergen desensitization therapy)



Order of Assessments / Procedures – Visit 1

- **Informed Consent**
- **Allocation of the subject number via IVRS/IWRS**
- Eligibility check before the assessments: Asthma diagnosis, demography, medical history, previous asthma treatments, concomitant medication
- ACQ
- Blood Pressure
- ECG
- Physical examination, body weight and height
- Blood sampling, urinalysis
- Skin Prick Test
- Pulmonary function tests (without bronchodilator for 6 hours)
  - Dispense of the e-diary, training and **e-diary PEF reference setting**
  - Pre-bronchodilator spirometry
  - Bronchodilation, using 400 µg of salbutamol – instruction of salbutamol and spacer use*
  - Post-bronchodilator spirometry (15-45 min after the bronchodilation)
  - Spirometry reversibility check
- Study Drug swallowing test
- Only for PK-CM sub-study: Holter cardiac monitoring (24 hours)
- Serious Adverse events

*Note: All patients will receive 1-2 salbutamol/albuterol MDI and a spacer device at Visit 1.

Order of Assessments / Procedures – Visit 2

- Eligibility check before the assessments: Asthma history, previous asthma treatments, medical history, concomitant medication
- ACQ, AQLQ(S), VAS nasal symptoms
- Blood Pressure
- ECG
- Physical examination
- Blood sampling, urinalysis
- Urine pregnancy test (women of childbearing potential – at least 16 days from Visit 1)
- Pulmonary function tests (without bronchodilator for 6 hours)
  - PEF diary review (at any time)
  - Pre-bronchodilator spirometry
  - Bronchodilation, using 400 µg of salbutamol
  - Post-bronchodilator spirometry (15-45 min after the bronchodilation)
  - Spirometry reversibility check
- **Randomization (Allocation of the randomization number via IVRS/IWRS)**
  - **OR Reporting screen failure**
- PikoLogic new setup for Visit 2 (or collecting PikoLogic for screen failures)
- Study drug dispensing
  - First dose of study drug taken at the site
  - Patients must remain at the site for 3 hours post dose for observation